

Article

Total Synthesis of the Norhasubanan Alkaloid Stephdiamine

Nina Hartrampf, Nils Winter, Gabriele Pupo, Brian M. Stoltz, and Dirk Trauner

J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 11 Jun 2018

Downloaded from <http://pubs.acs.org> on June 11, 2018

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.



ACS Publications

is published by the American Chemical Society, 1155 Sixteenth Street N.W., Washington, DC 20036

Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

Total Synthesis of the Norhasubanan Alkaloid Stephdiamine

Nina Hartrampf,^a Nils Winter,^a Gabriele Pupo,^c Brian M. Stoltz,^d and Dirk Trauner^{a,b*}

^aDepartment of Chemistry, University of Munich, Butenandtstraße 5-13, Munich 81377, Germany

^bDepartment of Chemistry, New York University, 100 Washington Square East, Room 712, New York, NY 10003,
Email: dirktrauner@nyu.edu

^cUniversity of Oxford, Chemistry Research Laboratory, 12 Mansfield Road, Oxford OX1 3TA, U.K.

^dWarren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

Supporting Information Placeholder

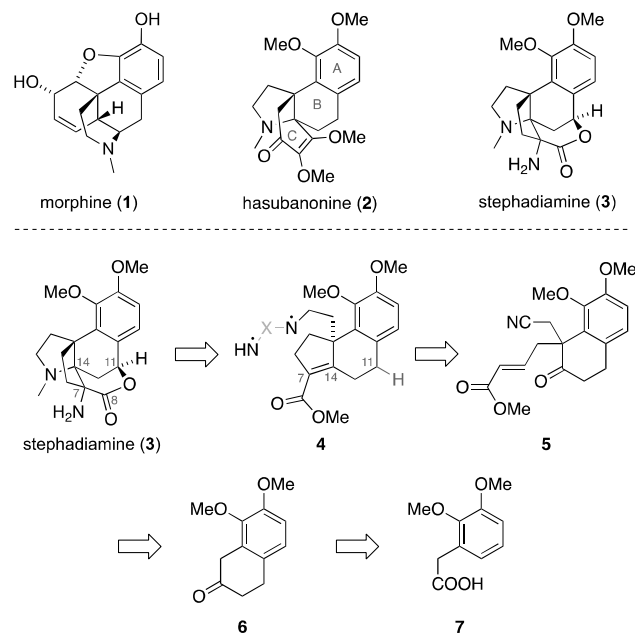
ABSTRACT: (+)-Stephdiamine is an unusual alkaloid isolated from the vine *Stephania japonica*. It features a norhasubanan skeleton, and contains two adjacent α -tertiary amines, which renders it an attractive synthetic target. Here, we present the first total synthesis of stephdiamine, which hinges on an efficient cascade reaction to implement the aza[4.3.3]propellane core of the alkaloid. The α -aminolactone moiety in a highly hindered position was installed via Tollens reaction and Curtius rearrangement. Useful building blocks for the asymmetric synthesis of morphine and (nor)hasubanan alkaloids are introduced.

INTRODUCTION. Morphine and hasubanan alkaloids have inspired synthetic chemists for decades. Following the pioneering work of Gates in 1952,^[1] more than 30 total and formal syntheses of morphine (**1**) have been published,^[2] some of them very recently.^[3] Many syntheses of hasubanonine (**2**) and its congeners have appeared in the literature since the isolation of the first hasubanan alkaloid was reported by Konto *et al.* in 1951.^[4] Therefore, it is surprising that one of the most beautiful and challenging molecules in the series, *viz.* stephdiamine (**3**), has been virtually ignored by the synthetic community.

(+)-Stephdiamine (**3**) was isolated from the snake vine *Stephania japonica* in 1984 by Taga *et al.* and is the only example of a norhasubanan alkaloid, which features a contracted C-ring.^[5] The absolute configuration of the natural product was elucidated by single crystal X-ray analysis of a benzoylated derivative of **3**. Although *S. japonica* is used in traditional Chinese medicine to treat asthma, fever and digestive disorders,^[6] the biological activity of stephdiamine (**3**) has yet to be established due to a paucity of material. Structurally, **3** features a unique pentacyclic skeleton arranged around an aza[4.3.3]propellane core. It bears a total of four stereocenters, including a benzylic quaternary carbon and two adjacent α -tertiary amines in a *cis*-1,2 relationship.^[7] One of these is part of an α -amino δ -lactone

which contains the benzylic oxygen often found in hasubanan alkaloids.

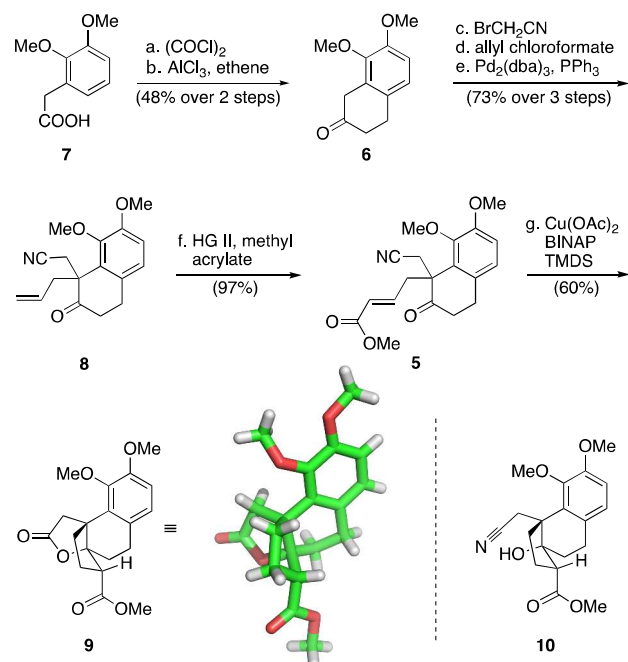
Scheme 1. Natural products related to stephdiamine and retrosynthesis.



INITIAL SYNTHETIC PLAN. Motivated by these unusual structural features and our general interest in hasubanan alkaloids,^[8] we set out to explore the synthesis of stephdiamine (**3**). Our initial strategy called for the installation of both α -tertiary amines and the [4.3.3]-azapropellane core through a late-stage and intramolecular *cis*-1,2-diamination (Scheme 1). The requisite diamination substrate **4**, a cyclopentene carboxylate, could be traced back to conjugated ester **5** *via* reductive aldol condensation. Ketone **5**, in turn, could be accessed from the known β -tetralone **6**.^[9] Tetralones with this substitution pattern are popular intermediates in the synthesis of hasubanan and morphinan alkaloids,^[10] but most reported preparations are lengthy, require expensive catalysts and starting materials, or are difficult to scale up.^[9] We therefore first set out to

develop a one-pot procedure starting from the commercially available carboxylic acid **7**.

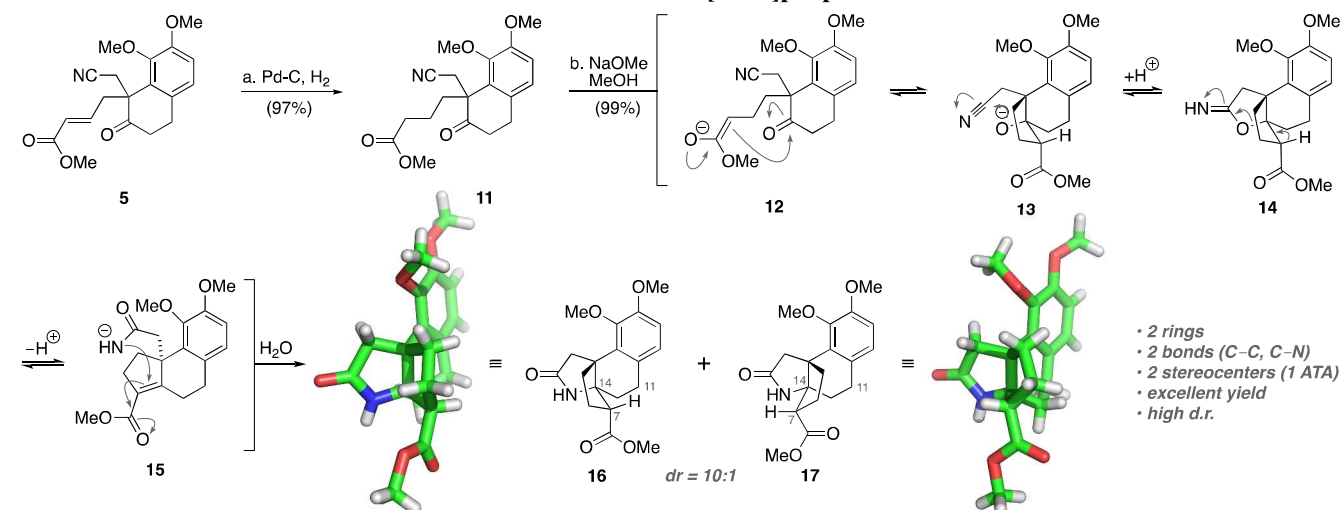
Scheme 2. Synthesis of tetralone **8** and attempted aldol condensation.



^aReagents and conditions: (a) oxalyl chloride (1.2 eq.), DMF (cat.), CH_2Cl_2 , 0 °C, 10 min, then r.t., 3 h; (b) AlCl_3 (6 eq.), ethene (1 atm), -32 °C, 6 h, 48% over 2 steps; (c) pyrrolidine (1.3 eq.), toluene, MgSO_4 , 100 °C, 24 h, then BrCH_2CN (1.6 eq.), 100 °C, 28 h, 89%; (d) NaH (1.1 eq.), THF, 0 °C, 30 min, then allyl chloroformate (1.0 eq.), 0 °C, 1 h, 98%; (e) $\text{Pd}_2(\text{dba})_3$ (2.5 mol%), PPh_3 (6.25 mol%), r.t., 12 h, 84%; (f) HG II (7 mol%), methyl acrylate (15 eq.), toluene, 48 h, 97%; (g) $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.5 eq.), *rac*-BINAP (0.5 eq.), TMSD (1 eq.), THF, r.t., 24 h \rightarrow 1 M HCl, r.t., 1 h, 60%. BINAP = 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl; dba = dibenzylideneacetone, HG II = Hoveyda-Grubbs cat. 2nd generation, TMSD = 1,1,3,3-tetramethyldisiloxane

Conversion of **7** to the corresponding acyl chloride, followed by treatment with AlCl_3 under an ethene atmosphere provided tetralone **6** in good overall yield and on a multi-gram scale (Scheme 2).^[9] Low temperatures were neces-

Scheme 3. Cascade reaction for the construction of the aza[4.3.3]propellane core.



sary in this reaction to prevent competing cyclization to the corresponding benzofuranone by participation of the adjacent methoxy group.^[11] Alkylation of **6** with bromoacetonitrile under Stork conditions,^[12] followed by conversion to the enol carbonate and decarboxylative Tsuji allylation yielded tetralone **8** as a racemate with the benzylic quaternary stereocenter in place.^[13] A subsequent cross metathesis with methyl acrylate then provided the conjugated ester **5** in excellent yield.^[14]

DISCOVERY OF A CASCADE REACTION. With ester **5** in hand, we investigated a reductive aldol reaction to form the five-membered ring.^[15] Using Stryker's reagent, we only isolated the 1,4-reduction product (**11**) accompanied by lactone **9**, which is presumably formed by attack of a tertiary alkoxide onto the nitrile followed by hydrolysis, and trace amounts of the anticipated aldol product **10**. Alternative hydride sources such as L-Selectride, $\text{Rh}(\text{cod})_2\text{OTf}/\text{PPh}_3/\text{H}_2$, and a copper hydride formed in situ from $\text{Cu}(\text{OAc})_2$, TMSD, and *rac*-BINAP only increased the yield of **9** (Scheme 2 and SI). The single crystal X-ray structure of **9** revealed a perfect *anti*-periplanar arrangement of the C-H bond next to the methyl ester and the lactone C-O bond. Despite this, we were unable to promote an elimination to the corresponding cyclopentene carboxylate.

Next, we attempted the aldol addition under conditions, which could enable the clean isolation of β -hydroxy ketone **10** with the nitrile intact (Scheme 2). In preparation for this, we hydrogenated **5** to obtain the saturated ester **11**. Upon exposure of **11** to *in situ* generated sodium methoxide in methanol at 75 °C, we isolated two new products in excellent combined yield. To our pleasant surprise, these were identified as the pyrrolidinone **16** and its C7-epimer **17**, both of which contain the aza[4.3.3]propellane core of stephadiamine (**3**) (Scheme 3). They are formed in a reaction cascade that presumably involves a transiently formed ester enolate **12**.

^aReagents and conditions: (a) Pd-C (10wt%), H₂ (1 atm), EtOAc, r.t., 12 h, 97%; (b) Na (1.2 eq.), MeOH, 75 °C, 24 h, 91% on 24 mmol scale, 99% on 3 mmol scale.

Intramolecular aldol addition then affords alkoxide **13**, which undergoes addition to the nitrile, elimination of the intermediary imidate (**14**→**15**), and conjugate re-addition in an aza-Michael reaction to yield the diastereomeric pyrrolidinones. This sequence of events resembles a cascade that was used in Inubushi's synthesis of cepharame, [16] although in our case we construct a different heterotricyclic system with an additional stereocenter in a remarkably efficient overall reaction.

INSTALLATION OF THE DIAMINE. At this point, completion of stephadiamine (**3**) formally required *N*-methylation, α -amination and closure of the lactone *via* benzylic functionalization. While the first task could be achieved by treating the diastereomeric mixture of lactams **16** and **17** with NaH and MeI, the second turned out to be exceedingly difficult due to the steric hindrance of the azapropellane system.

Attempted deprotonation of **16/17** and exposure to a variety of electrophilic amination reagents failed to give any identifiable products and mostly resulted in the recovery of starting materials. Similarly, carboxylation under a variety of conditions, which was intended to enable a Curtius rearrangement for the installation of the second α -tertiary amine, were unsuccessful. In addition, all efforts to epimerize the ester and to form a silyl ketene acetal failed, suggesting that the deprotonation step was the source of our frustrations.

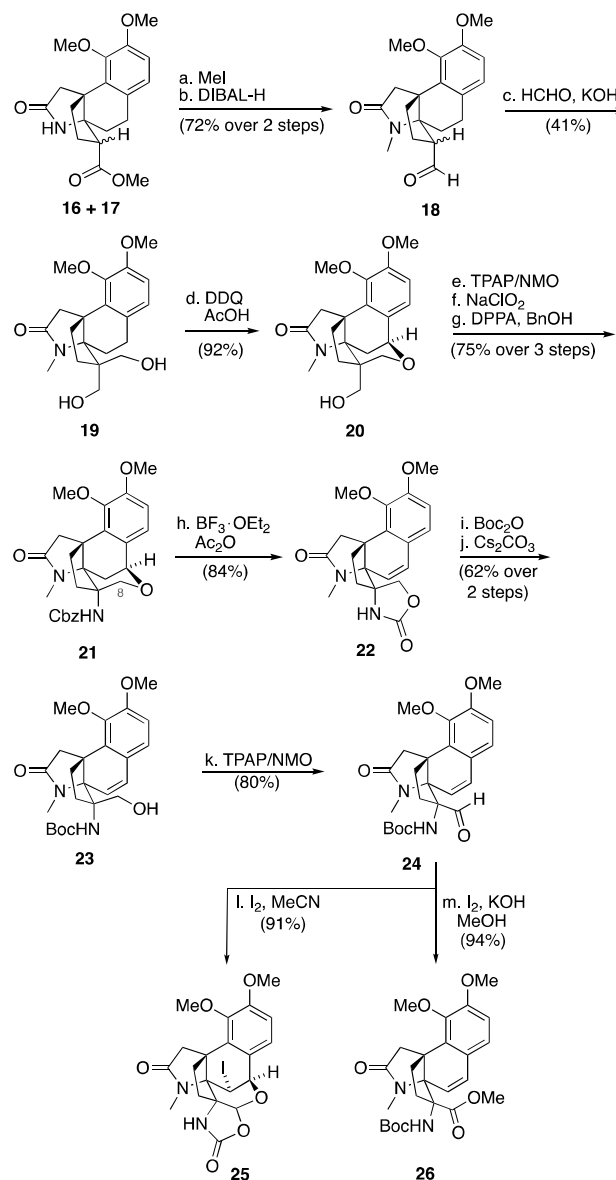
In an attempt to increase the acidity of the α -hydrogen, we reduced the ester moiety to the corresponding aldehyde **18** using DIBAL-H. Again, we only observed either decomposition or no reaction when we tried α -aminations or carboxylation reactions. We therefore decided to resort to chemistry that would employ one of the smallest base and electrophile combinations possible: the Tollens reaction (aldol reaction followed by crossed Cannizzaro reaction). [17] Exposure of aldehyde **18** to an excess of KOH and formaldehyde at elevated temperatures over two days afforded diol **19**, which features a quaternary carbon in a highly congested position.

To convert the 1,3-diol into the α -amino lactone moiety we tried to oxidize it to the corresponding malonate or carboxy lactone. This failed, as did our efforts to selectively protect one of the two primary alcohols. Therefore, we decided to differentiate them *via* benzylic oxidation. After screening multiple conditions, this could be accomplished using DDQ and AcOH at elevated temperatures yielding pyrane **20**. [18]

[18] With one hydroxymethyl group isolated, we turned to the implementation of the second α -tertiary amine. To this end, the primary alcohol **20** was converted to the carboxylic acid using Ley's conditions [19] followed by a Pinnick-Lindgren oxidation. [20] Formation of the acyl azide and subsequent Curtius rearrangement in the presence of benzyl

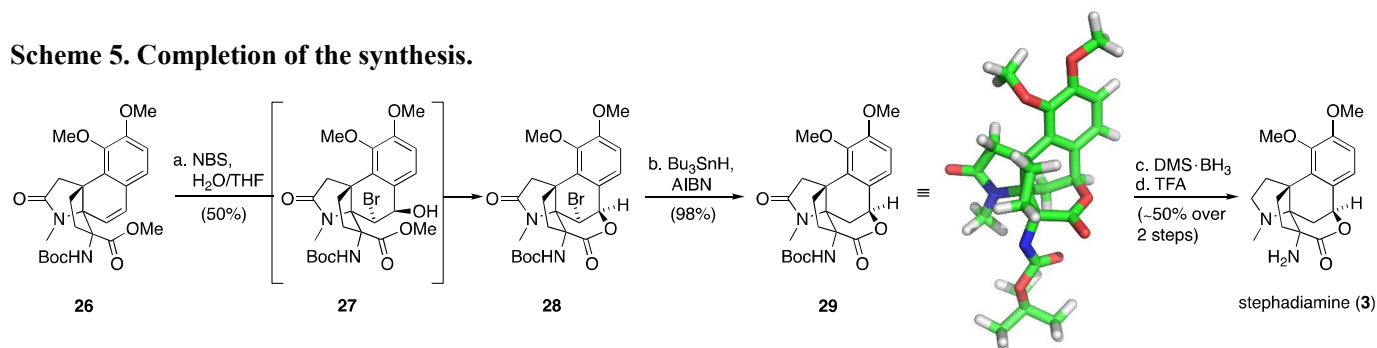
alcohol smoothly gave the Cbz-protected *cis*-1,2-diamine **21**.

Scheme 4. Installation of the diamine.



^aReagents and conditions: (a) NaH (1.2 eq.), MeI (1.2 eq.), DMF, 30 °C, 14 h, 91%; (b) DIBAL-H (2.5 eq.), CH₂Cl₂, -78 °C, 3.5 h, 79%; (c) KOH (10 eq.), formaldehyde (10 eq.), MeOH, 50 °C, 48 h, 41%; (d) DDQ (10 eq.), AcOH (10 eq.), 4 Å MS, DCE, 75 °C, 5 h, 92%; (e) TPAP (0.05 eq.), NMO (10 eq.), 4 Å MS, CH₂Cl₂, r.t., 1 h, 93%; (f) NaClO₂ (9.2 eq.), NaH₂PO₄ (9.2 eq.), 2-methyl-2-butene, *t*-BuOH/H₂O, r.t., 3 h, 96%; (g) DPPA (1.5 eq.), NEt₃ (3 eq.), toluene, r.t., 1 h, then 100 °C, 1 h, then BnOH (5 eq.), 100 h, 14 h, 84%; (h) BF₃·OEt₂ (30 eq.), Ac₂O, 0 °C to r.t., 6.5 h, 84%; (i) Boc₂O (2 eq.), NEt₃ (2 eq.), DMAP (0.1 eq.), THF, r.t., 17 h, 65%; (j) Cs₂CO₃ (0.5 eq.), MeOH, r.t., 12 h, 96%; (k) TPAP (0.02 eq.), NMO (4.5 eq.), 4 Å MS, CH₂Cl₂, r.t., 20 min, 80%; (l) I₂ (10 eq.), MeCN, r.t., 24 h, 91%; (m) I₂ (10 eq.), KOH (10 eq.), MeOH, r.t., 15 min, 94%. Cbz = carboxybenzyl, DIBAL-H = diisobutylaluminum hydride, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, MS = molecular sieves, TPAP = tetrapropyl-ammonium perruthenate, NMO = *N*-Methylmorpholine *N*-oxide, DPPA = diphenylphosphoryl azide, Boc = *tert*-butoxycarbonyl, DMAP = 4-dimethylaminopyridine.

Scheme 5. Completion of the synthesis.



^aReagents and conditions: (a) NBS (1.05 eq.), H₂O/THF, 0 °C, 90 min. then r.t., 90 min., 50%; (b) Bu₃SnH (10 eq.), AIBN (1 eq.), benzene, 90 °C, 3 h, 98%; (c) DMS·BH₃ (10 eq.), THF, 0 °C to r.t., 20 h, then 0 °C, AcOH, 57%, 99% brsm; (d) TFA, DCM, 0 °C, 90 min, <90%. NBS = *N*-bromosuccinimide, AIBN = α,α' -azoisobutyronitrile.

COMPLETION OF THE SYNTHESIS. At this stage, the completion of the synthesis would only require reduction of the lactam in **21**, oxidation of its tetrahydropyran to a lactone and deprotection of the primary amine. Although we were aware that chances were slim due to the presence of a benzylic C-H-bond and a very electron-rich rich aromatic ring, we first explored the oxidation under a variety of conditions (RuO₄, KMnO₄, CrO₃, DMDO, White–Chen catalyst).

Since none of the conditions led to any isolable products, we abandoned the direct oxidation of the ether **21** and decided to cleave the C11–O bond and oxidize C8 to the corresponding carboxylic acid followed by reclosure of the heterocycle. The reductive opening of benzylic ethers is a common transformation that can be achieved *via* hydrogenation or Lewis acid activation and hydride transfer.^[21] However, exposure of **21** to PtO₂/H₂, Pd-C/H₂, TFA/Et₃SiH or AcOH/Et₃SiH failed to promote the reductive cleavage of the C–O bond. We thus investigated different conditions for the conversion of the benzyl ether into the corresponding styrene via elimination. Since a variety of Lewis acids (TMSOTf, TMSCl, BF₃·OEt₂) in different solvents did not afford the desired product, we reasoned that the elimination could be reversible and added TFAA and Ac₂O to passivate the pendant alcohol. TFAA decomposed the starting material, but the use of excess BF₃·OEt₂ in acetic anhydride allowed for the isolation of oxazolidinone **22**. This compound was treated then with Boc₂O anhydride and then hydrolyzed to yield Boc-protected amino alcohol **23**.^[22]

The completion the synthesis required careful orchestration of redox reactions carried out on highly hindered and sensitive substrates. Ley oxidation of primary alcohol **23** to the corresponding aldehyde **24**, followed by attempted iodine mediated oxidation in acetonitrile, yielded the unusual oxazolidinone acetal **25**. Multiple standard oxidation conditions, led to similar products or resulted in decomposition. However, treatment with iodine in methanol cleanly yielded methyl ester **26**.^[23] Since this ester could not be hydrolyzed under a variety of conditions, we attempted the direct cyclization to lactone **28** or **29**. Acid-catalyzed lactonization and conventional halolactonizations were unsuccessful, presumably due to an unfavora-

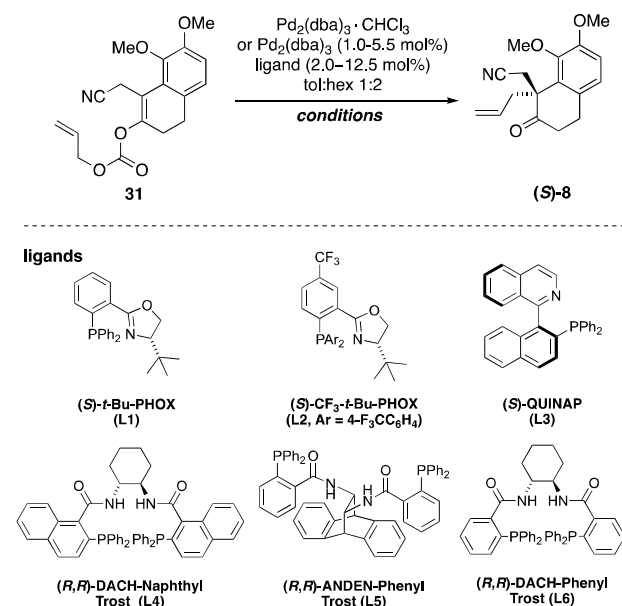
ble conformation of the ester. Using NBS in the presence of H₂O, however, we were able to regio- and stereoselectively install an intermediate bromohydrin **27**, characterized by mass spectrometry, which subsequently underwent lactonization.^[24] The secondary bromide of the resultant halolactone **28** was removed under radical conditions to obtain the pentacyclic lactone **29**, the structure of which was confirmed by single X-ray analysis. In the final steps of the synthesis, the lactam moiety in **29** was reduced to the corresponding pyrrolidine using borane dimethyl sulfide complex.^[25] Close monitoring of the reaction was crucial to avoid competing reduction of the strained yet sterically hindered six-membered lactone. Acidic deprotection of the primary amine finally gave racemic stephamine (**3**). The deprotection step was carried out in deuterated dichloromethane and monitored by NMR as slow cleavage of the lactone was observed upon exposure to TFA. The analytical data of synthetic **3** were in complete agreement with the limited data available from the original publication.

ASYMMETRIC APPROACH. In parallel to our racemic synthesis, we investigated an asymmetric approach to (+)-stephamine. Since the benzylic quaternary stereocenter directs the formation of all others stereocenters, we focused on the asymmetric allylation of **3**. Formation of a chiral imine/enamine and reaction with a variety of electrophiles was unsuccessful.^[26] Therefore, we turned toward modern transition metal catalysis to install the benzylic quaternary stereocenter (Scheme 4).^[27] The asymmetric Tsuji allylation was investigated with a variety of chiral ligands such as (*S*)-*t*-Bu-PHOX (**L1**), (*S*)-CF₃-*t*-Bu-PHOX (**L2**), (*S*)-QUINAP (**L3**), (*R,R*)- and (*S,S*)-DACH-Phenyl Trost ligand (**L4**), (*R,R*)-DACH-Naphthyl Trost ligand (**L5**) and (*R,R*)-ANDEN-Phenyl Trost ligand (**L6**, Table 1). These were used in different solvents and at varying concentrations and temperatures. In an initial screening, we found that a 1:2 mixture of toluene and hexane was the best solvent, providing the highest *ee* value across all ligand classes. The starting material was consumed in all cases and no side-products were observed.

The ligand (*S*)-*t*-Bu-PHOX only gave 6% *ee*, whereas the electron-deficient congener (*S*)-CF₃-*t*-Bu-PHOX provided 38% *ee* (entries 1 and 2). (*S*)-QUINAP gave a very low *ee*

of 11% (entry 3), whereas the C_2 -symmetric (*R,R*)-DACH-Phenyl Trost ligand gave the highest *ee* value (entry 6). Related Trost ligands resulted in a decrease of *ee* values (entries 4 and 5). Therefore, we decided to optimize the reaction for the DACH-Phenyl Trost ligand. It was found that keeping the ligand/ $\text{Pd}_2(\text{dba})_3$ ratio exactly to 2.2:1 was crucial to obtain a good *ee* (entry 5). In additional experiments, we determined that when using this ligand, the reaction went to completion within minutes and therefore the reaction time could be shortened to 5 min (entry 6). Ultimately, treatment of the allylic carbonate **31** with $\text{Pd}_2(\text{dba})_3$ in the presence of chiral bis-phosphine *ent*-**L6** gave (*R*)-**8** in 97% yield and 66% *ee* (see SI for details).^[28] After a single recrystallization we obtained an almost enantiomerically pure product, the absolute configuration of which could be established by X-ray crystallography.

Table 1 Optimization of conditions for the asymmetric decarboxylative Tsuji allylation.



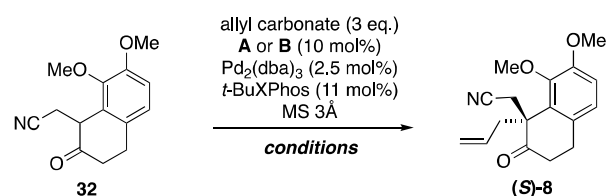
Entry	ligand	[M]	T [°C]	time [min]	<i>ee</i>
1	L1	0.03	rt	120	6%
2	L2	0.03	rt	120	38%
3 ^{a)}	L3	0.03	rt	120	11%
4	L4	0.03	rt	120	29%
5	L5	0.03	rt	120	27%
6	L6	0.03	–10	120	59%

7	L6	0.03	–10	120	66%
8 ^{a)b)}	<i>ent</i> -L6	0.003	–10	5	66%

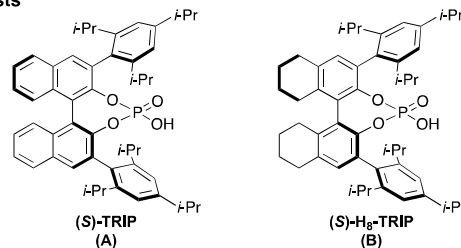
^a(*R*)-**8** was observed as the major enantiomer. ^bConditions: enol carbonate (1.0 equiv), $\text{Pd}_2(\text{dba})_3$ or $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (4–10 mol%), ligand (7–12 mol%) in 1:2 toluene:hexane, in glovebox. the reaction gave the desired (*R*)-enantiomer in 97% yield. The enantiomeric excess of this sample could be enriched to 98% *ee* after recrystallization

In an effort to improve the enantioselectivity of the reaction, we turned our attention towards enol catalysis, which was recently introduced by List and co-workers^[29] and allows for the direct regio- and enantioselective functionalization of unsymmetrical ketones. This is achieved by employing a chiral phosphoric acid, which selectively forms the most substituted enol, followed by asymmetric reaction with an appropriate electrophile. Under the previously reported conditions,^[27b] which employ a palladium (0) source and (*S*)-TRIP (cat. **A**) as a catalyst, **32** reacted smoothly with allyl methyl carbonate (>95% conversion, entry 1, Table 2). The desired product (*S*)-**8** was isolated in 84% enantiomeric excess. Upon switching to (*S*)-H₈-TRIP (cat. **B**) as a catalyst, we were able to increase the enantioselectivity to 86% *ee* (entry 3).

Table 2 Optimization of conditions for the direct asymmetric α -allylation via enol catalysis.



catalysts



Entry ^{a)}	catalyst	[M]	T [°C]	time [min]	<i>ee</i>
1	A	0.05	rt	18	84%
2	A	0.025	rt	18	85%
3	B	0.05	rt	18	86%
4	B	0.025	rt	36	88%

5	B	0.01	rt	96	89%
6	B	0.025	15	96	89%
7 ^{b)}	B	0.025	15	96	88.5%
8 ^{c)}	B	0.01	15	96	93%
9 ^{d)}	ent-B	0.02	10	96	90%

^aConditions: allyl carbonate (1.0 equiv), Pd₂(dba)₃ (2.5 mol%), chiral acid catalyst A or B (10 mol%), *t*-BuXPhos (11 mol%) in cyclohexane. Full conversion by ¹H-NMR was observed unless otherwise noted. (a) Methylcyclohexane was used as solvent; (b) 63% conversion (determined by ¹H NMR), 63% isolated yield; (c) 85% conversion (determined by ¹H NMR), 81% isolated yield

Upon further optimization of the reactions conditions, the desired product was isolated in 63% yield (97% brsm) and 93% *ee* (entry 8) or in 81% yield (96% brsm) with 90% *ee* (entry 9).

CONCLUSIONS. In summary, we have achieved the first synthesis of the unusual alkaloid stephadiamine (**3**), in racemic form. Our synthesis is marked by a practical β -tetralone synthesis, the facile construction of the benzylic quaternary center through twofold alkylation, and a remarkably efficient cascade to forge the azapropellane core of **3**. The installation of the α -amino lactone moiety proved to be difficult but could eventually be achieved using a very small base and electrophile. It also required a carefully orchestrated sequence of oxidation and reductions in a densely functionalized setting. Finally, we have elaborated a pathway for the asymmetric synthesis of stephadiamine. The building blocks developed in this context, (**R**)-**8** and (**S**)-**8**, could serve as valuable intermediates in the synthesis of a variety of hasubanan and morphine alkaloids, respectively.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: XXXX.

Experimental procedures, spectroscopic data and copies of NMR-spectra (PDF). CIF file for compounds **5** (CCDC 1823787), **6** (CCDC 1823794), (*rac*)-**8** (CCDC 1823788), (**R**)-**8** (CCDC 1823795), (**S**)-**8** (CCDC 1823796), **9** (CCDC 1823789), **11** (CCDC 1823792), **16** (CCDC 1823793), **17** (CCDC 1823791), **20** (CCDC 1823800), **21** (CCDC 1823798), **22** (CCDC 1823799), **29** (CCDC 1823801), **32** (CCDC 1823786), **S1** (CCDC 1823790), **S2** (CCDC 1823797), (CIF files are also available free from charge on [## AUTHOR INFORMATION](https://www.ccdc.cam.ac.uk/structures/>(CIF))</p>
</div>
<div data-bbox=)

Corresponding Author

*dirktrauner@nyu.edu

ORCID

Dirk Trauner: 0000-0002-6782-6056

Brian M. Stoltz: 0000-0001-9837-1528

Nina Hartrampf: 0000-0003-0875-6390

Gabriele Pupo: 0000-0003-3084-3888

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We would like to acknowledge Dr. Anastasia Hager and Dr. Dominik Hager for their contributions in the early stages of this project. The authors thank Dr. Hong-Dong Hao and Dr. Julius R. Reyes for experimental assistance, Dr. Scott Virgil and René Rahimoff for assistance with HPLC and Dr. Peter Mayer for X-ray structure analysis. Additionally, we acknowledge the Deutsche Telekom Foundation (Ph.D. fellowship to N.H.), the LMUMentoring program (fellowship N.H.), the Otto Bayer Scholarship (fellowship to N.H.) as well as the Deutsche Forschungsgemeinschaft (SFB 749 and CIPSM) for generous funding. B.M.S. thanks the NIH-NIGMS (R01GM080269) for partial financial support of this project. Dr. Felix Hartrampf and Dr. Julius R. Reyes are acknowledged for excellent support in the course of this project and with the preparation of this manuscript.

REFERENCES

- [1] M. Gates, G. Tschudi, *J. Am. Chem. Soc.* **1956**, *78*, 1380-1393.
- [2] a) U. Rinner, T. Hudlicky, In *Alkaloid Synthesis*; H.-J. Knölker, Eds.; Springer: Berlin, Heidelberg, **2012**; b) N. Chida, in *Chemistry of Opioids*, Vol. 299 (Ed.: H. Nagase), Springer-Verlag Berlin, Berlin, **2011**, pp. 1-28; c) U. Rinner, T. Hudlicky, *Top. Curr. Chem.* **2012**, *309*; d) J. W. Reed, T. Hudlicky, *Acc. Chem. Res.* **2015**, *48*, 674-687.
- [3] a) M. Ichiki, H. Tanimoto, S. Miwa, R. Saito, T. Sato, N. Chida, *Chem. Eur. J.* **2013**, *19*, 264-269; b) J. Li, G.-L. Liu, X.-H. Zhao, J.-Y. Du, H. Qu, W.-D. Chu, M. Ding, C.-Y. Jin, M.-X. Wei, C.-A. Fan, *Chem. Asian J.* **2013**, *8*, 1105-1109; c) M. Geffe, T. Opatz, *Org. Lett.* **2014**, *16*, 5282-5285; d) M. Tissot, R. J. Phipps, C. Lucas, R. M. Leon, R. D. M. Pace, T. Ngouansavanh, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2014**, *53*, 13498-13501; e) S. Chu, N. Münster, T. Balan, M. D. Smith, *Angew. Chem. Int. Ed.* **2016**, *55*, 14306-14309; f) H. Umihara, S. Yokoshima, M. Inoue, T. Fukuyama, *Chem. Eur. J.* **2017**, *23*, 6993-6995; g) J. Rautschek, A. Jäger, P. Metz, *Org. Lett.* **2018**, *20*, 832-835.
- [4] a) H. S. Kondo, Masakichi; Odera, Toshiko *Ann. Rept. ITSU Lab.* **1951**, *2*, 35-43; b) M. Tomita, T. Ibuka, Y. Inubushi, Y. Watanabe, M. Matsui, *Tetrahedron Lett.* **1964**, *5*, 2937-2944; c) M. Tomita, T. Ibuka, Y. Inubushi, Y. Watanabe, M. Matsui, *Chem. Pharm. Bull.* **1965**, *13*, 538-545; d) Y. Inubushi, T. Ibuka, In *The Alkaloids*; R. H. F. Manske, Eds.; Academic Press: New York **1977**; e) M. Matsui, In *The Alkaloids*; A. Brossi, Eds.; Academic Press, New York, **1988**. f) S. M. King, S. B. Herzon, In *The Alkaloids*; H.-J. Knölker, Eds.; Academic Press, Burlington, **2014**.
- [5] T. Taga, N. Akimoto, T. Ibuka, *Chem. Pharm. Bull.* **1984**, *32*, 4223-4225.
- [6] a) G. E. W. Tang, *Chinese Drugs of Plant Origin: Chemistry, Pharmacology, and Use in Traditional and Modern Medicine*

- Springer, Berlin Heidelberg, **2013**; b) Y. X. F. Bingyi, C. Anmin, M. Yingfu, S. Fang, Q. Jinlin, G. Yuan, G., L. Q. Zheming, W. Shu, *Encyclopedic Reference of Traditional Chinese Medicine*, Springer, Berlin Heidelberg, **2013**.
- [7] A. Hager, N. Vrielink, D. Hager, J. Lefranc, D. Trauner, *Nat. Prod. Rep.* **2016**, *33*, 491-522.
- [8] G. Volpin, N. A. Vepřek, A. B. Bellan, D. Trauner, *Angew. Chem. Int. Ed.* **2017**, *56*, 897-901.
- [9] a) M. D. Soffer, R. A. Stewart, J. C. Cavagnol, H. E. Gellerson, E. A. Bowler, *J. Am. Chem. Soc.* **1950**, *72*, 3704-3709; b) G. B. Diamond, M. D. Soffer, *J. Am. Chem. Soc.* **1952**, *74*, 4126-4127; c) M. A. McKervey, S. M. Tuladhar, M. F. Twohig, *J. Chem. Soc., Chem. Commun.* **1984**, 129-130; d) Á. Gorka, B. Czuczai, P. Szoleczky, L. Hazai, C. Szántay, V. Háda, C. Szántay, *Synth. Commun.* **2005**, *35*, 2371-2378; e) D.-H. Wang, K. M. Engle, B.-F. Shi, J.-Q. Yu, *Science* **2010**, *327*, 315-319; f) E. V. Cabrera, A. C. Gil, J. G. Ortega, L. Bedoya, J. Sánchez, A. K. Banerjee, *Org. Prep. Proced. Int.* **2011**, *43*, 364-367.
- [10] a) D. A. Evans, C. A. Bryan, C. L. Sims, *J. Am. Chem. Soc.* **1972**, *94*, 2891-2892; b) J. Mulzer, G. Dürner, D. Trauner, *Angew. Chem. Int. Ed.* **1996**, *35*, 2830-2832; c) D. Trauner, *Synthesis* **1998**, *1998*, 653-664; d) J. D. White, P. Hrnčiar, F. Stappenbeck, *J. Org. Chem.* **1999**, *64*, 7871-7884; e) T. X. Nguyen, Y. Kobayashi, *J. Org. Chem.* **2008**, *73*, 5536-5541.
- [11] J. H. Burckhalter, J. R. Campbell, *J. Org. Chem.* **1961**, *26*, 4232-4235.
- [12] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, R. Terrell, *J. Am. Chem. Soc.* **1963**, *85*, 207-222.
- [13] a) J. Tsuji, I. Minami, I. Shimizu, *Tetrahedron Lett.* **1983**, *24*, 1793-1796; b) J. Tsuji, I. Shimizu, I. Minami, Y. Ohashi, T. Sugiura, K. Takahashi, *J. Org. Chem.* **1985**, *50*, 1523-1529; c) J. Tsuji, I. Minami, *Acc. Chem. Res.* **1987**, *20*, 140-145.
- [14] a) A. K. Chatterjee, J. P. Morgan, M. Scholl, R. H. Grubbs, *J. Am. Chem. Soc.* **2000**, *122*, 3783-3784. b) J. S. Kingsbury, J. P. A. Harrity, P. J. Bonitatebus, A. H. Hoveyda, *J. Am. Chem. Soc.* **1999**, *121*, 791-799.
- [15] H. Nishiyama, T. Shiomi, in *Metal Catalyzed Reductive C–C Bond Formation: A Departure from Preformed Organometallic Reagents* (Ed.: M. J. Krische), Springer Berlin Heidelberg, Berlin, Heidelberg, **2007**, pp. 105-137.
- [16] a) Y. Inubushi, T. Ibuka, M. Kitano, *Tetrahedron Lett.* **1969**, *10*, 1611-1614; b) Y. Inubushi, M. Kitano, T. Ibuka, *Chem. Pharm. Bull.* **1971**, *19*, 1820-1841.
- [17] [17] a) J. Yu, X. Z. Wearing, J. M. Cook, *J. Org. Chem.* **2005**, *70*, 3963-3979; b) M. B. Smith, J. March, *March's advanced organic chemistry: reactions, mechanisms, and structure*; John Wiley & Sons: Hoboken, New Jersey, **2007**.
- [18] H. Yi, Q. Liu, J. Liu, Z. Zeng, Y. Yang, A. Lei, *ChemSusChem* **2012**, *5*, 2143-2146.
- [19] W. P. Griffith, S. V. Ley, G. P. Whitcombe, A. D. White, *J. Chem. Soc., Chem. Commun.* **1987**, 1625-1627.
- [20] a) Lindgren, B. O.; Nilsson, T., *Acta Chem. Scand.* **1973**, *27*, 888-890; b) G. A. Kraus, M. J. Taschner, *J. Org. Chem.* **1980**, *45*, 1175-1176; c) B. S. Bal, W. E. Childers, H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091-2096.
- [21] S. A. Weissman, D. Zewge, *Tetrahedron* **2005**, *61*, 7833-7863.
- [22] S. J. Baker, K. J. M. Beresford, D. W. Young, *Tetrahedron* **2014**, *70*, 7221-7228.
- [23] a) W. A. Ayer, W. R. Bowman, G. A. Cooke, A. C. Soper, *Tetrahedron Lett.* **1966**, *7*, 2021-2026; b) S. Yamada, D. Morizono, K. Yamamoto, *Tetrahedron Lett.* **1992**, *33*, 4329-4332.
- [24] V. L. Rendina, S. A. Goetz, A. E. Neitzel, H. Z. Kaplan, J. S. Kingsbury, *Tetrahedron Lett.* **2012**, *53*, 15-18.
- [25] a) M. Robba, D. Maume, *Tetrahedron Lett.* **1972**, *13*, 2333-2335; b) W.-H. Meng, T.-J. Wu, H.-K. Zhang, P.-Q. Huang, *Tetrahedron: Asymmetry* **2004**, *15*, 3899-3910; c) J.-X. Du, H.-Y. Huang, P.-Q. Huang, *Tetrahedron: Asymmetry* **2004**, *15*, 3461-3466.
- [26] a) M. Pfau, G. Revial, A. Guingant, J. d'Angelo, *J. Am. Chem. Soc.* **1985**, *107*, 273-274; b) S. Giroux, E. J. Corey, *Org. Lett.* **2008**, *10*, 5617-5619.
- [27] M. Mahlau, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 518-533.
- [28] a) J. Tsuji, I. Shimizu, I. Minami, Y. Ohashi, *Tetrahedron Lett.* **1982**, *23*, 4809-4812; b) D. C. Behenna, B. M. Stoltz, *J. Am. Chem. Soc.* **2004**, *126*, 15044-15045; c) B. M. Trost, J. Xu, *J. Am. Chem. Soc.* **2005**, *127*, 2846-2847; d) J. T. Mohr, B. M. Stoltz, *Chem. Asian J.* **2007**, *2*, 1476-1491; e) B. M. Trost, J. Xu, T. Schmidt, *J. Am. Chem. Soc.* **2009**, *131*, 18343-18357.
- [29] a) I. Felker, G. Pupo, P. Kraft, B. List, *Angew. Chem. Int. Ed.* **2015**, *54*, 1960-1964; b) G. Pupo, R. Properzi, B. List, *Angew. Chem. Int. Ed.* **2016**, *55*, 6099-6102; c) M. R. Monaco, G. Pupo, B. List, *Synlett* **2016**, *27*, 1027-1040.

Graphic Table of Contents (TOC)

